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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,761	08/28/2000	Vivienne Frances Cox	088362/0113	2793

7590 05/23/2002

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 05/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,761	COX ET AL.	
	Examiner	Art Unit	
	Dave Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-44* is/are pending in the application.

4a) Of the above claim(s) *35-38 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Applicant's election with traverse of Group I claims, claims 22-34 and 39-42 in the response filed December 21, 2001 has been acknowledged. Because applicant did not distinctly and specifically point out the supposed error in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 35-38, 43, 44 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 22-34 and 39-42 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-34 and 39-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only for claims directed to:

A nucleic acid sequence encoding at least one autonomously folding polypeptide domain or at least one immunogenic polypeptide, wherein the sequence comprises a linear concatamer of at least two non-identical DNA sequences, wherein the non-identical DNA sequence each encodes the same amino acid sequence coding for the autonomously folding polypeptide domain or the polypeptide;

A composition comprising a pharmaceutically acceptable carrier and the nucleic acid sequence as described in the immediately preceding paragraph; and

A method for delivering the composition to a mammal, the method comprising administering the composition to the mammal.

The specification does not reasonably provide enablement for any other claimed embodiment as embraced by the presently pending claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims when given a broadest reasonable interpretation encompass a genus of an unspecified polypeptide that is encoded by a linear concatamer of at least two non-identical DNA sequences, wherein the non-identical DNA sequence each encodes the same amino acid sequence of a polypeptide. However, the as-filed specification only provides sufficient guidance for enabling claims directed to a nucleic acid sequence encoding at least one autonomously folding polypeptide domain or at least one immunogenic polypeptide, wherein the sequence comprises a linear concatamer of at least two non-identical DNA sequences, wherein the non-identical DNA sequence each encodes the same amino acid sequence coding for the autonomously folding polypeptide domain or the polypeptide. Other than the essential feature of the invention is the making and use of a linear concatamer of DNA sequences coding for multidomain proteins containing extended repetitive sequences, particularly those useful for the creation of molecular adjuvants and immunogens, the as-filed specification does not provide sufficient guidance as how to use other linear concatamer containing DNA sequences for any purpose. As such, it is not apparent how one skilled in the art, without undue experimentation, how to practice the claimed invention as broadly claimed, particularly on the basis of applicant's disclosure. Notwithstanding the lack of reasonable enablement for the claimed subject matter as broadly claimed in the presently pending claims, claims 41-44 also embrace any pharmaceutical compositions containing any linear concatamer of nucleic acid sequences for use as a drug within the context of DNA therapeutic application in any mammal, let alone any animal or human. Major considerations for any nucleic acid therapy protocol involve issues that include:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA complexes to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

4/ The fraction of vector taken up by the target cell population, the trafficking of the nucleic acid within cellular organelles, the rate of degradation of the nucleic acid, the level of mRNA produced, the stability of the nucleic acid product, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced; and

4/ What amount is considered to be therapeutically effective for a nucleic acid therapy method.

In addition, all of these issues differ dramatically based on the specific carrier used, the nucleic acid being used and the disease being treated.

More specifically, Anderson, Nature, Vol. 392, pp. 25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). In addition, Verma *et al.,* Nature Vol. 389, pp. 239-242, 1997, states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, column 1), and that one major obstacle to success has been the ability to deliver genes efficiently and obtain sustained expression (page 239, column 3).

Given that *in vivo* nucleic acid therapy wherein any carrier including naked DNA comprising any linear concatamer is employed to correct a disease or a medical condition in any and/or all mammals remains unpredictable at the tine the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any or all of the polynucleotide sequences cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to determine as to which of the DNA containing composition would exhibit a "pharmaceutical effect" as intended for use in therapeutic application in any animal including a human.

The presently pending claims also encompass pharmaceutical DNA containing compositions for

use in the form of DNA vaccine for use in any animal, *e.g.,* reptiles, birds, amphibians, insects, fish, mammal, and humans. The state of the art exemplified by McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) indicates:

- "The route of deliver of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thu8s potentially on the nature of the immune response" (page 295, column 1bridging column 2);
- "More recent with antigen-encoding plasmids have shown that antigen expression does not continue indefinitely, but rather is lost by some immune-mediated mechanism around 2-3 weeks after DNA injection" (page 295, column 2, last paragraph); and
- A number of factors appear to influence the Th bias of the immune response, including (i) the angigen; (ii) the dose of antigen; (iii) whether the antigen is secreted, cytoplasmic, or membrane bound; (iv) the route and method of DNA administration; (v) the number of immunizations; (vi) the presence of CpG motifs; (vii) the haplotype of the mouse immunized; (viii) the presence of adjuvant; (ix) co-expression of cytokines; (x) whether DNA is formulated (e.g., with cationic liposomes); and (xi) rest period between immunizations (page 296, column 1).

Even if an animal model including a mouse model may show a desire immune response (CTL responses) by art-recognized intramuscular injection route, McCluskie *et al.* teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition and as to mucosal routes as embraced by the claims, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that

"although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

In view of the reasonable unpredictability of the state of the art of DNA immunization methods as indicated in the exemplified McCluskie *et al.* reference, one skilled in the art then turns this instant specification for guidance, however, other than simple making of Bac vectors expressing a linear concatamer coding for the C3 fragment C3d, the as-filed specification including the working examples does not provide sufficient guidance and/or evidence to overcome the obstacles as disclosed in the state of the prior art. As such, it is not apparent as to how a skilled artisan practices the claimed invention as broadly claimed, particularly on the basis of applicant's disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-34 and 39-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "at polypeptide" on line 1 of each of claims 22, 23, and on claims dependent there from is indefinite because it is not apparent the "at polypeptide" is grammatically incorrect and appears to be a typo mistake. In view of compact prosecution, the term is intended to mean "a polypeptide". In addition, the recitation of "a polypeptide" on line 4 of each of claims 22 and 23 is vague since it is not apparent how the term is related structurally to the "at polypeptide" described in the preamble of the claim. Furthermore, the phrase "the same amino acid sequence of a polypeptide" is indefinite and/or lacks a proper antecedent basis because the phrase could be interpreted as any of unspecified amino sequences obtained from "a polypeptide". Should

applicant intend to mean "the same amino acid sequence coding for a polypeptide", such change is required to obviate the rejection. In addition, the "comprises codes" are grammatically incorrect. Appropriate correction is required. In addition, the "each encode" is grammatically incorrect. The "each encode" should be corrected as "each encodes".

In claim 25, the term "corresponding" is indefinite because it is not apparent as to what standard the "corresponding" is intended to be embraced by the claim. Should applicant intend to refer to a particular polypeptide referred earlier in the base claim, the base claim perhaps should be amended to recite numerically such that the "corresponding" can be amended to "the first" or "the second polypeptide", for example.

Claim 29 is dependent from the base claim 22. However, claim 22 does not recite any polypeptide ligand. As such, the "polypeptide ligand" cited in claim 29 lacks a proper antecedent basis.

All dependent claims in reciting "A" in the beginning of the claim renders the claims indefinite because it is not apparent as to which of the sequences, vectors, host cells, or methods cited in the base claim, the "A" refers to. A change from "A" in each of the dependent claims to -- The -- would obviate the rejection.

Claim 43 is indefinite because the preamble of the claim particularly recites the intended use of "inducing an immune response to an antigen", however, the concatamer of claim 22 does not recite any material(s) that exhibits or are linked structurally to the intended use. As such, the claim appears to be incomplete or does not contain active step(s) or material(s) linked positively to the preamble of the claim. Also, the term "the human" lacks a proper antecede basis.

Claim 44 is indefinite for the same reasons as set forth in the immediately preceding paragraph. Claim 44 recites administering the pharmaceutical composition of claim 42. However, the composition does not recite any material(s) that is linked structurally or functionally to the required preamble of claim 44, which is to induce an immune response. Furthermore, it is not apparent as to which material(s) the immune response is desired for induction.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22, 24, 30, 31, 32, 41, 42 are rejected under 35 USC 102(b) as being anticipated by Ferrari *et al.* (US Pat NO. 5,641,648).

To the extent that claims are interpreted as a host cell comprising an expression vector comprising a DNA sequence encoding a polypeptide, wherein the sequence comprises a concatamer of nucleic acid sequences, wherein each of the nucleic acid sequences encodes a repeating unit of 30 amino acid resides, and wherein the nucleic acid sequences are not the same, Ferrari *et al.* teach identical products throughout the patent disclosure, particularly columns 3-4, columns 5-6, 7-8

Absent evidence to the contrary, Ferrari *et al.* anticipates the claims.

Claims 22, 24, 30, 31, 32, 41-44 are rejected under 35 USC 103(a) as being unpatentable over any of Matsunaga (US Pat No. 5,861,285), Eilers *et al.* (US Pat NO. 6,265,562) and Whitlow (US Pat NO. 5,767,26), taken with Ferrari *et al.*

To the extent that claims are interpreted as a host cell comprising an expression vector comprising a DNA sequence encoding two polypeptides wherein each polypeptide comprises at least 30 amino acid residues, wherein the sequence comprises a concatamer of nucleic acid sequences, Matsunaga teaches the same throughout the patent disclosure, particularly columns 4, 5, and 19. In addition, Eilers *et al.* teach the same on column 11. Whitlow teaches the same on columns 5-7. Matsunaga, Eilers *et al* and Whitlow do not teach that the nucleic acid sequences coding for the two polypeptides are not identical. However, at the time the invention was made, Ferrari taught that concatamers can be routinely made and that DNA sequences coding for repeating unites of amino acids resides can be non-identical, and that repeating units having the same nucleotide residues present in a concatamer is unstable during the recombinant production, and that by making the DNA sequences non-identical, the concatamer is more stable for production of a desire polypeptide.

It would have been obvious for one of ordinary skill in the art to make the nucleic acid sequences contained in the vector construct of Matsunaga, Eilers *et al.*, or Whitlow being non-identical. One would have been motivated to do so because of the disclosure of Ferrari, which teaches that repeating units having the same nucleotide residues present in a concatamer is unstable during the recombinant production, and that by making the DNA sequences non-identical, the concatamer is more stable for production of a desire polypeptide.

Thus, the claimed invention *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 22, 24-28, 33, 34, 39, 40 are rejected under 35 USC 103(a) as being unpatentable over any of Matsunaga (US Pat No. 5,861,285), Eilers *et al.* (US Pat NO. 6,265,562) and Whitlow (US Pat NO. 5,767,26), taken with Ferrari *et al.*, and further in view of Kimizuka *et al.* (US Pat No. 5,049,658).

The rejection under 35 USC 103(a) of the base claims as being unpatentable over any of Matsunaga, Eilers *et al.* and Whitlow is applied here as indicated above. To the extent that the combined cited references do not teach incorporation of a peptide linker encoding DNA linker comprising a cystein encoding codon at the C-terminus of one of the polypeptide or repeating unit, the concept of using cystein encoding codon or linker for the purpose of linking to a desire antigen or any protein of interest is routine and conventional in the prior art of DNA recombinant techniques, as evidenced by Kimizuka *et al.* (column 4). A skill artisan would have been motivated to employ a peptide linker encoding DNA comprising a cystein coding codon in the making of the concatamer of the combined cited references. The skilled artisan would have been motivated to do so because the prior art of record exemplified by Kimizuka *et al.* discloses that concept of using cystein encoding codon or linker for the purpose of linking to a desire antigen or any protein of interest is routine and conventional in the prior art of DNA recombinant techniques and because one would have been motivate to make a fusion protein comprising a unpaired cystein for the purpose of creating a convenient linkage site so as to link to any desire antigen or protein of interest.

Thus, the claimed invention *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 23, 29 are free of the prior art of record.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER